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April 19, 2012

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, MD 20852

Dear Dr. Hamburg,

Public Citizen, representing more than 250,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA) 21 U.S.C. § 355(e) and 21 C.F.R. 10.30, to immediately remove from the market the diabetes drug liraglutide (Victoza; Novo Nordisk) because the known increased risks of thyroid cancer and pancreatitis, both of which occurred in people enrolled in preapproval clinical trials, outweigh any documented clinical benefits.

The FDA pharmacology reviewers concluded, prior to liraglutide's approval, that it was not approvable due to its induction of thyroid C-cell tumors in animals at drug exposures similar to drug exposures seen in people taking the drug.

No information concerning the mechanism for this tumor-inducing effect of the drug in animals could rule out a similar risk to humans. The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) agreed that it could not rule out the thyroid as a possible target organ for neoplasm induction in people. To the question, "Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?" 12 committee members voted "no," including both thyroid cancer experts; there was only one "yes" vote.[1] There was the additional problem of how to monitor patients for preneoplastic effects as well as thyroid tumors.

[1] FDA Clinical Safety Review. Web page 139. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.

The FDA clinical safety reviewer concurred with the conclusions of the pharmacology team but added an additional concern: the unknown risk of major cardiovascular events, such as cardiovascular death, myocardial infarction, or stroke. Both cardiologists and the biostatistician on the advisory committee agreed, stating that, because of trial design deficiencies in assessing cardiovascular risk in preapproval trials, it was not possible to rule out unacceptable excess cardiovascular risk relative to comparator drugs.

Between January 2010, the month of liraglutide's FDA approval, and June 2011, the FDA has, in fact, issued new warnings on pancreatitis, thyroid C-cell tumors, and worsening renal function, including acute renal failure associated with the use of liraglutide. Public Citizen's analysis of the Adverse Event Reporting System (AERS) database (from Febuary 2010 through September 2011) found 200 cases of acute pancreatitis and 28 cases of pancreatic cancer, as well as 26 cases of thyroid tumors, reported to the FDA by people using liraglutide.

I. BACKGROUND

A. FDA-approved indications

Victoza (liraglutide) was approved January 25, 2010, for the treatment of type 2 diabetes in those patients who had failed to achieve glucose control after trying diet, exercise, and other drugs for diabetes. That is, this drug is not recommended as first-line therapy for any patients who have inadequate glycemic control on diet and exercise.[2] Because it is a peptide that would be broken down in the stomach if administered orally, liraglutide must be given as a subcutaneous (SQ) injection.

B. Description

Liraglutide is a 32 amino acid peptide analog of native (natural) human glucagon-like peptide-1 (GLP-1) that functions as an agonist (activator) at the GLP-1 receptor (GLP-1R). The native GLP-1 has been modified with one amino acid substitution (lysine replaced by arginine) and the addition of a fatty acid (palmitic acid), making it resistant to degradation (by peptidase). This chemical structure also promotes self-association (a molecule sticking to part of itself), leading to slower absorption and high protein binding. These modifications result in a major lengthening of the time, compared to native GLP-1, that liraglutide can remain active in the body — from minutes to days. The half-life for native GLP-1 is less than two minutes, while liraglutide, the modified form, has a half-life of 13 hours.[3] This results in only 2% of the native GLP-1 remaining after 12 minutes, while it would take three days for liraglutide to reach that 2% level.

C. Mechanism of action

Liraglutide's use in terms of diabetes treatment involves its ability to improve glycemic control by increasing insulin synthesis and secretion by the pancreas, as well as by inhibiting glucagon secretion (which, if not inhibited, would otherwise increase glucose levels). Through effects via

[2] Novo Nordisk Inc. Victoza drug label. Web page 5. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 20, 2012.
[3] Novo Nordisk Inc. Victoza drug label. Web page 5. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 16, 2012.

nerve endings in the intestinal wall that transmit signals to the central nervous system, liraglutide, as a GLP-1 agonist, would also be expected to slow both acid secretion and gastric emptying of the stomach and decrease food consumption.[4]

However, the actions of liraglutide on the gastrointestinal (GI) tract also include significant adverse impacts on patients. The most common adverse effects seen in subjects treated with liraglutide (and at rates much higher than seen with comparator drugs) are GI in origin: nausea (up to 35% of subjects), vomiting, diarrhea, dyspepsia, and constipation.[5]

D. Distribution of GLP-1Rs

The sponsor would predictably like the focus on liraglutide functions to be limited to its beneficial effects on the stomach, as well as on insulin and glucagon secretion. However, since the GLP-1R, to which GLP-1 and liraglutide bind, is "widely distributed throughout the body (e.g.[,] alpha, beta, delta cells of the pancreas, peripheral and central nervous system, heart, kidney, type II pneumocytes [cells in the lung responsible for production and secretion of surfactant], parietal cells [cells in the stomach that secrete acid]),"[6] many other effects are biologically plausible.

Additional effects of liraglutide and other GLP-1R agonists include an improvement in memory (seen in healthy male mice and male mice from a strain used as a model of Alzheimer's disease),[7,8] increases in blood pressure and heart rate (seen in adult male rats and healthy young adults),[9,10] and modulation of bone resorption by stimulating the release of calcitonin (an inhibitor of bone resorption; seen in male mice).[11]

The presence of GLP-1Rs in many human tissues, both normal and cancerous, can be demonstrated by autoradiography of radioactive ^{125}I-GLP-1 binding.[12] Tables 1-3 (which the FDA pharmacology reviewer took from the medical literature) show GLP-1 binding to human tumors of the endocrine system, the central nervous system, and embryonic tissue (Table 1) and normal tissue from the thyroid, pancreas, lung, central nervous system, GI tract, and kidney. The

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[4] Williams DL Minireview: finding the sweet spot: peripheral *versus* central glucagon-like peptide 1 action in feeding and glucose homeostasis. Endocrinology. 2009;150:2997-3001.

[5] Novo Nordisk Inc. Victoza drug label. Web page 3. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 16, 2012.

[6] Davis-Bruno K. FDA memorandum from Pharmacology Supervisor to NDA 22-341. July 13, 2009.Web page 7. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

[7] McClean PL, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci. 2011;31:6587-6594.

[8] Porter DW, Kerr BD, Flatt PR, et al. Four weeks administration of liraglutide improves memory and learning as well as glycaemic control in mice with high fat dietary-induced obesity and insulin resistance. Diabetes Obes Metab. 2010;12:891-899.

[9] Yamamoto H, Lee CE, Marcus JN, et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. J Clin Invest. 2002;110:43-52.

[10] Edwards CMB, Todd JF, Ghatei MA, Bloom SR. Subcutaneous glucagon-like peptide-I (7-36) amide is insulinotropic and can cause hypoglycaemia in fasted healthy subjects. Clin Sci. 1998;96:719-724.

[11] Yamada C, Yamada Y, Tsukiyama K et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology. 2008;149:574-579.

[12] FDA Pharmacology Review. Web pages 90-91. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed February 16, 2012.

FDA reviewer highlighted binding in medullary thyroid carcinomas (Table 1), a normal thyroid, and normal pancreas (Tables 2 and 3).

TABLE 1
GLP-1 Receptor Incidence and Density in Human Tumors

Tumor type	GLP-1 receptor incidence*	GLP-1 receptor density†
Endocrine tumors		
Pheochromocytomas	12/20 (60)	3,970 ± 1,002
Paragangliomas	5/18 (28)	1,353 ± 601
Medullary thyroid carcinomas	5/18 (28)	1,326 ± 264
Adrenal cortical adenomas	0/7 (0)	
Parathyroid carcinomas	0/4 (0)	
Pituitary adenomas	0/36 (0)	
Tumors of nervous system		
Meningiomas	7/20 (35)	989 ± 271
Astrocytomas	4/16 (25)	1,069 ± 398
Glioblastomas	2/21 (9)	790 ± 120
Ependymomas	1/6 (16)	1,075
Schwannomas	0/9 (0)	
Embryonic tumors		
Medulloblastomas	3/12 (25)	1,246 ± 728
Nephroblastomas	2/9 (22)	421 ± 21
Neuroblastomas	3/16 (18)	932 ± 518
Carcinomas		
Ovarian adenocarcinomas	2/12 (16)	688 ± 364
Prostate carcinomas	1/20 (5)	1,283
Breast carcinomas	0/22 (0)	
Colorectal adenocarcinomas	0/21 (0)	
Gastric adenocarcinomas	0/20 (0)	
Pancreatic adenocarcinomas	0/21 (0)	
Cholangiocellular carcinomas	0/17 (0)	
Hepatocellular carcinomas	0/16 (0)	
Non–small cell lung carcinomas	0/20 (0)	
Small cell lung carcinomas	0/6 (0)	
Renal cell carcinomas	0/20 (0)	
Non–Hodgkin's lymphomas	0/10 (0)	

*Values in parentheses are percentages.
†Mean ± SEM of receptor-positive cases (dpm/mg tissue).

[Körner M et al., . J Nucl Med 48: 736–743, 2007]

TABLE 3
GLP-1 Receptor (GLP-1 R) Expression in Lung and Thyroid Gland of Rat, Mouse, and Human: Comparison of Receptor Incidence and Density

Organ	GLP-1 R	Rat*	Mouse*	Human*
Lung	Incidence	3/3 (100)	6/6 (100)	11/28 (39)
	Density†	3,477 ± 1,539	1,677 ± 439	636 ± 164
Thyroid gland	Incidence	12/12 (100)	3/5 (60)	1/18 (6)
	Density†	2,289 ± 282	1,982 ± 470	1,193

*Values in parentheses are percentages.
†Mean ± SEM of receptor-positive cases (dpm/mg tissue).

TABLE 2
GLP-1 Receptor Density in Receptor-Positive Human Normal Tissues

Organ	Tissue compartment	GLP-1 receptor density*
Central nervous system	Neurohypophysis	5,207 ± 472 (n = 6)
	Leptomeninges	1,453 ± 276 (n = 6)
Normal pancreas	Islets	1,322 ± 143 (n = 24)
	Acini	693 ± 49 (n = 9)
Chronic pancreatitis	Islets	960 ± 251 (n = 6)
	Acini	567 ± 112 (n = 6)
Duodenum	Brunner's glands	2,752 ± 522 (n = 5)
Ileum	Myenteric plexus	887 ± 285 (n = 6)
Colon	Myenteric plexus	788 ± 84 (n = 9)
Breast	Ducts and lobuli	519 ± 136 (n = 3)
Lung	Small blood vessels	636 ± 164 (n = 11)
Kidney	Large- and medium-sized arteries	674 ± 127 (n = 2)

*Mean ± SEM of receptor-positive cases (dpm/mg tissue).

[Körner M et al., . J Nucl Med 48: 736–743, 2007]

II. EFFICACY OF LIRAGLUTIDE

Novo Nordisk submitted five pivotal phase 3 clinical trials in support of the application for approval. One trial was 52 weeks in length; the other four were 26 weeks each (see Table 4).[13]

Table 4. Pivotal Clinical Trials for Liraglutide

Statistical review of NDA 022341/0 Liraglutide for type 2 diabetes 10/65

TABLE 1 Overview of treatment regimens in the five therapeutic confirmatory trials

Trial	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Placebo	Active Comparator
1573	N/A	Liraglutide 1.2 mg + placebo (glimepiride)	Liraglutide 1.8 mg + placebo (glimepiride)	N/A	Glimepiride 8 mg + placebo (liraglutide)
1572	Liraglutide 0.6 mg + placebo (glimepiride) + metformin 2 g	Liraglutide 1.2 mg + placebo (glimepiride) + metformin 2 g	Liraglutide 1.8 mg + placebo (glimepiride) + metformin 2 g	Placebo (liraglutide) + placebo (glimepiride) + metformin 2 g	Glimepiride 4 mg + placebo (liraglutide) + metformin 2 g
1436	Liraglutide 0.6 mg + placebo (rosiglitazone) + glimepiride 4 mg	Liraglutide 1.2 mg + placebo (rosiglitazone) + glimepiride 4 mg	Liraglutide 1.8 mg + placebo (rosiglitazone) + glimepiride 4 mg	Placebo (liraglutide) + placebo (rosiglitazone) + glimepiride 4 mg	Rosiglitazone 4 mg + placebo (liraglutide) + glimepiride 4 mg
1574	N/A	Liraglutide 1.2 mg + metformin 2 g + rosiglitazone 8 mg	Liraglutide 1.8 mg + metformin 2 g + rosiglitazone 8 mg	Placebo (liraglutide) + metformin 2 g + rosiglitazone 8 mg	N/A
1697	N/A	N/A	Liraglutide 1.8 mg + glimepiride 4 mg + metformin 2 g	Placebo (liraglutide) + glimepiride 4 mg + metformin 2 g	Insulin glargine + glimepiride 4 mg + metformin 2 g

Doses of metformin and glimepiride could be adjusted in Trial 1572 (metformin 1.5–2 g), Trial 1436 (glimepiride 2–4 mg) and Trial 1697 (glimepiride 2–4 mg).
N/A: not assessed

The primary end point of the trials was the decline in levels of hemoglobin A1c (HbA1c, hemoglobin with a glucose sugar attached),[14] which served as an indicator of long-term glucose

[13] FDA briefing document for the April 2, 2009 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Web page 139. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM148645.pdf. Accessed February 16, 2012.
[14] FDA Clinical Review; Web page 41; Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 20, 2012.

levels in the blood. Most studies of drugs for diabetes use HbA1c as the surrogate end point for benefit.

All trials were randomized, double-blind, and parallel-group, testing either different doses of liraglutide or comparing liraglutide (one or more doses) to other drugs for diabetes. In some of the trials, subjects administered liraglutide also simultaneously received other diabetes drugs.

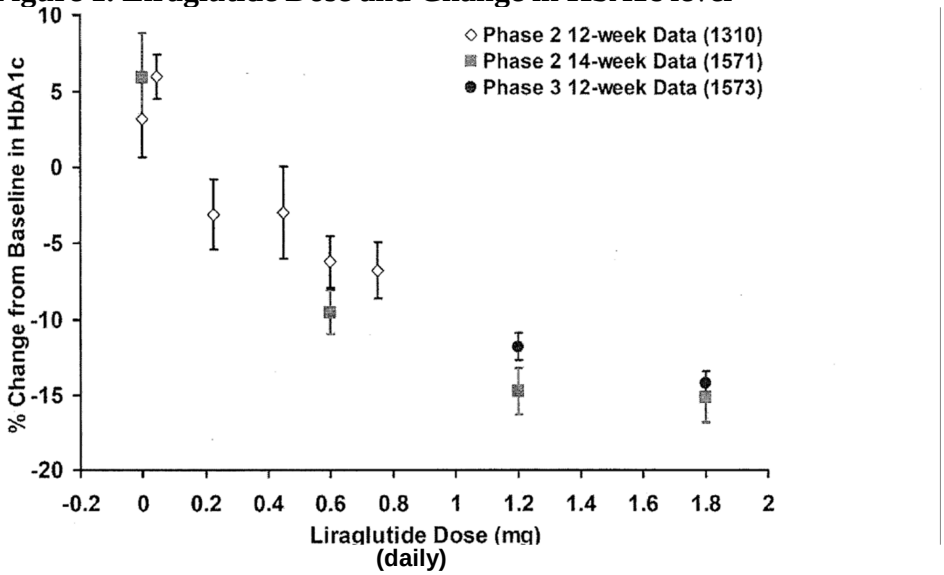
The key efficacy results from the pivotal clinical trials are presented in Table 5. It is interesting that there is so little difference in the percent change from baseline in the HbA1c levels between the two different doses in the three 26-week studies where both doses were studied. Figure 1 shows the leveling off of effect on HbA1c levels with increasing dose from 1.2 milligrams (mg) to 1.8 mg.[15]

Table 5. Efficacy Summary of Pivotal Phase 3 Studies[16]

	Change from baseline (% HbA1c)				
Study number, duration, and drugs tested	**Liraglutide 0.6 mg/day**	**Liraglutide 1.2 mg/day**	**Liraglutide 1.8 mg/day**	**Comparator**	**Placebo**
1573 (52 wks.) alone or glimepiride alone	Not done	-0.84	-1.14	-0.51	Not done
1572 (26 wks.) +glimepiride + metformin and glimepiride + metformin	-0.70	-0.97	-1.00	-0.99	0.08
1436 (26 wks.) + glimepiride and glimepiride + rosiglitazone	-0.60	-1.08	-1.13	-0.44	0.23
1574 (26 wks.) + metformin + rosiglitazone	Not done	-1.48	-1.48	Not done	-0.54
1697 (26 wks.) +glimepiride +metformin and: insulin + glimepiride + metformin	Not done	Not done	-1.33	-1.09	-0.24

[15] FDA Clinical Pharmacology Review. Web page 37. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000clinpharmr.pdf . Accessed February 16, 2012.
[16] FDA Statistical Review. Web page 44. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000statr.pdf. Accessed February 16, 2012

Figure 1. Liraglutide Dose and Change in HbA1c level



III. SAFETY (ANIMAL TOXICITY)

A. Effects on the thyroid in rats and mice

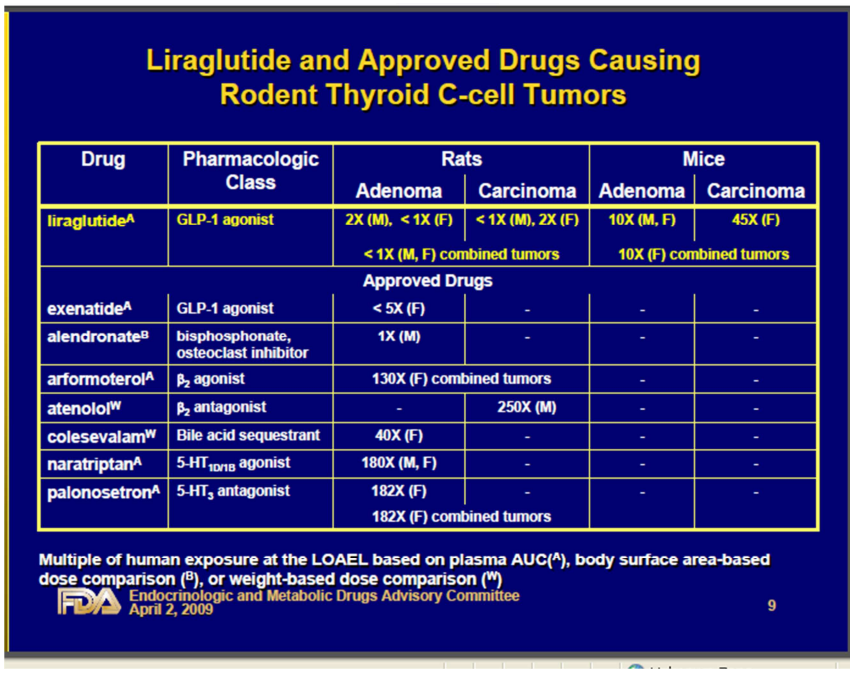
The major safety issue with liraglutide, raised by FDA pharmacologists, came from the rodent carcinogenicity studies, where statistically significant drug-related increases in thyroid tumors occurred in two species (mice and rats) and both genders (male and female) at drug exposures similar to those seen in patients taking the maximum recommended human dose of 1.8 mg/day.

In fact, liraglutide is the only drug approved by the FDA that causes thyroid C-cell tumors (adenomas and carcinomas) in both sexes of rats and mice. The FDA searched all drug labels for approved drugs, as well as its internal databases, and could "not identify any other approved or investigational drug causing thyroid c-cell tumors in mice."[17] In terms of outcomes in rats, no other FDA-approved drug caused C-cell tumors in both sexes of rats. Where tumors did occur in rats, most did so at much higher multiples of the human exposure, with the exceptions of alendronate (1x) and exenatide (<5x), the other FDA-approved GLP-1 agonist,[18] (Table 6).

[17] FDA briefing document for the April 2, 2009, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Web page 22. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM148645.pdf. Accessed February 16, 2012.

[18] FDA presentation slides for the April 2, 2009 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, slide #9. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM151129.pdf. Accessed February 16, 2012.

Table 6. C-cell Tumors in Rats and Mice



Liraglutide and Approved Drugs Causing Rodent Thyroid C-cell Tumors

Drug	Pharmacologic Class	Rats		Mice	
		Adenoma	Carcinoma	Adenoma	Carcinoma
liraglutide[A]	GLP-1 agonist	2X (M), < 1X (F)	< 1X (M), 2X (F)	10X (M, F)	45X (F)
		< 1X (M, F) combined tumors		10X (F) combined tumors	
Approved Drugs					
exenatide[A]	GLP-1 agonist	< 5X (F)	-	-	-
alendronate[B]	bisphosphonate, osteoclast inhibitor	1X (M)	-	-	-
arformoterol[A]	β_2 agonist	130X (F) combined tumors		-	-
atenolol[W]	β_2 antagonist	-	250X (M)	-	-
colesevalam[W]	Bile acid sequestrant	40X (F)	-	-	-
naratriptan[A]	5-$HT_{1D/1B}$ agonist	180X (M, F)	-	-	-
palonosetron[A]	5-HT_3 antagonist	182X (F)	-	-	-
		182X (F) combined tumors			

Multiple of human exposure at the LOAEL based on plasma AUC([A]), body surface area-based dose comparison ([B]), or weight-based dose comparison ([W])

FDA Endocrinologic and Metabolic Drugs Advisory Committee April 2, 2009

9

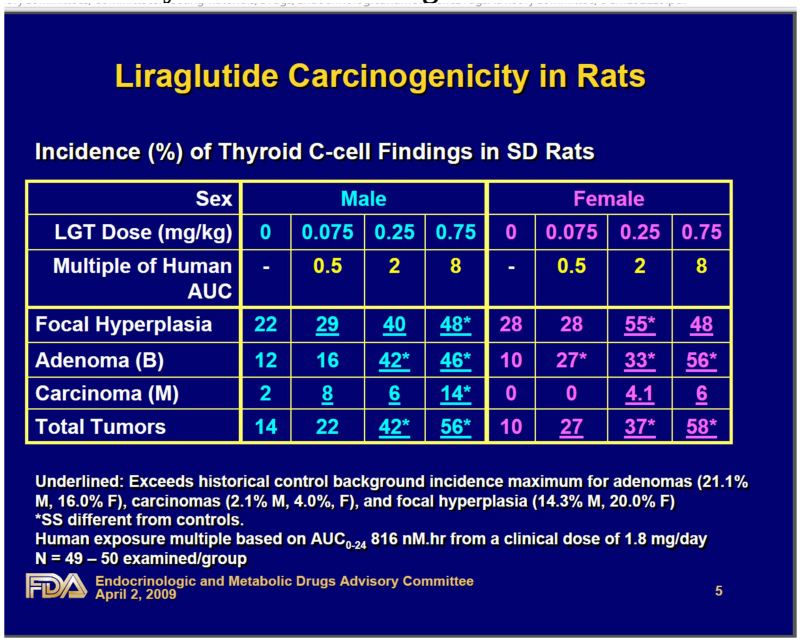
1. Rat carcinogenicity[19]

The rates of abnormal thyroid C-cell findings (hyperplasia or tumors) in liraglutide-treated rats were higher than historical control background rates for adenomas (occurring at exposures only two times those used in humans, based on a clinical dose of 1.8 mg/day, for both male and female rats), carcinomas (occurring at doses only 0.5 times human exposure in male rats and two times human exposure in female rats), and focal hyperplasia (occurring at exposures 0.5 times human exposure in male rats and two times human exposure in female rats) (Table 7).

There was "no observed effect level" established for rats. That is, there was no tested dose at which increased rates of thyroid tumors were not seen. Moreover, for both male and female rats, the rate of abnormal C-cell thyroid findings increased as the dose increased from 0.5 times human exposure to eight times human exposure.

[19] FDA presentation slides for the April 2, 2009, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for liraglutide slides, slide# 5. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM151129.pdf. Accessed February 16, 2012.

Table 7. Thyroid C-cell Findings in Rats



Liraglutide Carcinogenicity in Rats

Incidence (%) of Thyroid C-cell Findings in SD Rats

Sex	Male				Female			
LGT Dose (mg/kg)	0	0.075	0.25	0.75	0	0.075	0.25	0.75
Multiple of Human AUC	-	0.5	2	8	-	0.5	2	8
Focal Hyperplasia	22	29	40	48*	28	28	55*	48
Adenoma (B)	12	16	42*	46*	10	27*	33*	56*
Carcinoma (M)	2	8	6	14*	0	0	4.1	6
Total Tumors	14	22	42*	56*	10	27	37*	58*

Underlined: Exceeds historical control background incidence maximum for adenomas (21.1% M, 16.0% F), carcinomas (2.1% M, 4.0%, F), and focal hyperplasia (14.3% M, 20.0% F)
*SS different from controls.
Human exposure multiple based on AUC_{0-24} 816 nM.hr from a clinical dose of 1.8 mg/day
N = 49 – 50 examined/group

FDA Endocrinologic and Metabolic Drugs Advisory Committee
April 2, 2009

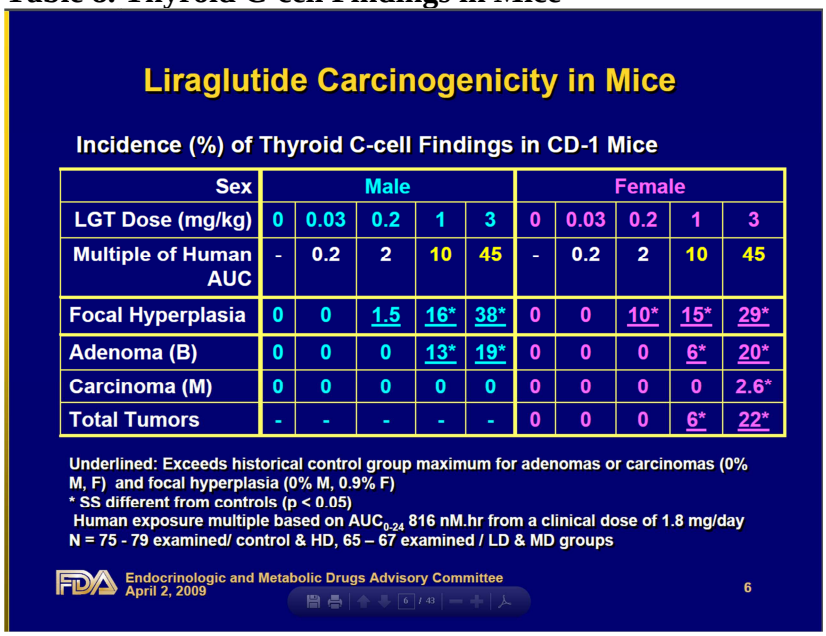
5

2. Mouse carcinogenicity[20]

The rates of abnormal C-cell thyroid findings in liraglutide-treated mice were higher than historical control background rates for adenomas for both male and female mice (at exposures 10 times those used in humans, based on a clinical dose of 1.8 mg/day) and focal hyperplasia for both male and female mice (at exposures two times those used in humans). The rate of adenomas plus carcinomas was statistically significantly higher than both the historical control background rate and the concurrent controls (in females) at 10 times human exposures (Table 8).

[20] FDA presentation slides for the April 2, 2009 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for liraglutide slides, slide# 6. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM151129.pdf. Accessed February 16, 2012.

Table 8. Thyroid C-cell Findings in Mice



Liraglutide Carcinogenicity in Mice

Incidence (%) of Thyroid C-cell Findings in CD-1 Mice

Sex	Male					Female				
LGT Dose (mg/kg)	0	0.03	0.2	1	3	0	0.03	0.2	1	3
Multiple of Human AUC	-	0.2	2	10	45	-	0.2	2	10	45
Focal Hyperplasia	0	0	1.5	16*	38*	0	0	10*	15*	29*
Adenoma (B)	0	0	0	13*	19*	0	0	0	6*	20*
Carcinoma (M)	0	0	0	0	0	0	0	0	0	2.6*
Total Tumors	-	-	-	-	-	0	0	0	6*	22*

Underlined: Exceeds historical control group maximum for adenomas or carcinomas (0% M, F) and focal hyperplasia (0% M, 0.9% F)
* SS different from controls ($p < 0.05$)
Human exposure multiple based on $AUC_{0\text{-}24}$ 816 nM.hr from a clinical dose of 1.8 mg/day
N = 75 - 79 examined/ control & HD, 65 – 67 examined / LD & MD groups

FDA Endocrinologic and Metabolic Drugs Advisory Committee April 2, 2009

6

B. Effects on the GI tract[21]

In animal studies, GI adverse effects of liraglutide included transient decreased food consumption in mice, rats, and monkeys — although the effect was dose-limiting in rats.

C. Effects on blood cells[22]

Decreased red blood cell counts, hematocrit, and hemoglobin occurred in mice, rats, and monkeys at "clinically relevant doses" of liraglutide. The largest statistically significant hematologic changes in monkeys were increases in blood eosinophils of 300% in males (at 60 times the human exposure) and 600%, 1,200%, and 1,600% increases in females at 0.6 times, six times, and 60 times human exposure, respectively, based on body surface area.[23]

D. Effects on the cardiovascular system

Liraglutide increased the heart rate in isolated rabbit hearts, increased heart rate and cardiac output in a pig model of myocardial infarction, and, in rats, increased systolic, diastolic, and mean arterial blood pressure at exposures equal to or greater than two times the human exposure (at the 1.8 mg/day dose).[24]

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[21] FDA Pharmacology Review. Web page 94. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.
[22] FDA Pharmacology Review. Web page 17. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.
[23] FDA Pharmacology Review. Web page 155. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.
[24] FDA Pharmacology Review. Web page 299. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 23, 2012.
[23a] FDA Pharmacology Review. Web page 300. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

E. Effects on the kidney

According to the pharmacology review, "Liraglutide had effects on kidneys in mice, rats, and monkeys."[23a] In studies of rats given radioactive liraglutide, radioactivity accumulated in the kidneys, increasing over time to a peak at seven days post-dose (last day measured), which implies that the drug, and/or its metabolites, accumulates in the kidney and could interfere with kidney function.[25]

Following a single 5 mg/kg dose of liraglutide, diuresis (increase in urine volume) occurred in mice, along with increased excretion of sodium, phosphate, and chloride and decreased excretion of magnesium, potassium, and calcium. These changes were "considered pharmacological effects of liraglutide."[26] There was also a diuretic effect in water-loaded rats administered single doses of liraglutide (0.2 or 2 mg/kg): urine volume, sodium, potassium, and chloride excretion increased.[25a]

F. Effects on the pancreas

In rats exposed to liraglutide, "the incidence of minimal focal [pancreatic] inflammation was increased in high dose females."[27] Such inflammation would be consistent with pancreatitis. Pancreatic beta cell proliferation occurred in obese diabetic mice and rats exposed to the drug. In nondiabetic female rats at eight times the human exposure of liraglutide, there was mild pancreatic acinar cell atrophy with focal inflammation (also comparable to pancreatitis).[28]

In monkeys given liraglutide, the increased weight of the pancreas correlated with an increased mass of pancreatic exocrine cells and ducts (beginning at the lowest dose tested, which was equivalent to human exposure based on body surface area). Since this increased mass was quantified only at the highest drug dose tested (5 mg/kg), it is again not possible to know the lowest dose at which these effects first appeared.[29]

G. Radiolabeled drug levels in rat tissues

Rats were given a single SQ dose of 0.15 mg per kg of ^{3}H-labeled liraglutide and were killed at the times indicated in Table 9 (one and four hours and one, two, and seven days post-dose). Tissue drug levels were quantitated and expressed as a ratio to plasma levels. Ratios continued to rise with time after dose, up to the last day tested (either two or seven days post-dose) in all tissues measured. Higher tissue levels of the drug might have occurred at higher doses.

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[25] FDA Pharmacology Review.
Web page 72. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

[26] FDA Pharmacology Review. Web page 96. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

[25a] FDA Pharmacology Review. Web page 30. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

[27] FDA Pharmacology Review. Web page 97. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

[28] FDA Pharmacology Review. Web page 300. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 23, 2012.

[29] FDA Pharmacology Review. Web page 1. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed February 16, 2012.

[28a] FDA Pharmacology Review. Web page 72. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 16, 2012.

Unfortunately, there were no data for tissue levels in the pancreas. Note that the drug is present in the thyroid gland and kidney, two target organs of toxicity.[28a]

Table 9. Radiolabeled Liraglutide Distribution in Rat Tissues

Tissue Distribution of ^{3}H-[Pal]-Liraglutide in Albino Sprague Dawley Rats

Liraglutide Dose (mg/kg), [Radionuclide]	Sex / Sample Time (h)	Males 1	Males 4	Males 24	Males 48	Males 168	Females 1	Females 4	Females 24	Females 48	Females 168
0.15, [^{3}H-Pal] (sc dosing)	Plasma, dry (ng equiv / g)	42	125	87	21	1	50	192	76	13	1
	Plasma Radioactivity Concentration Ratio										
	Adrenal	0.4	0.4	1.2	-	30.0	0.3	-	1.2	6.3	-
	Fat (brown)	-	0.1	1.4	5.8	42.0	-	0.2	2.0	6.3	16.0
	Kidney	0.4	0.3	1.2	3.2	22.0	0.4	0.3	1.4	4.8	13.0
	Liver	0.4	0.7	2.1	4.0	11.0	0.4	0.7	2.0	5.2	8.0
	Ovary	-	-	-	-	-	0.2	0.2	4.5	-	-
	Preputial gland	-	-	2.0	27.9	-	-	-	4.4	46.8	-
	Small Intestine wall	-	0.1	1.8	3.2	-	-	0.2	1.6	4.4	9.0
	Thyroid	-	0.2	1.0	2.3	23.0	-	0.1	0.9	5.2	14.0

H. Effects on reproductive toxicity: fetal anomalies and malformations in rats and rabbits

Liraglutide, given to pregnant rats and rabbits, caused malformations at very low drug exposures. In female rabbits, malformations occurred at liraglutide exposures below human exposure (at a dose of 1.8 mg/day), and in rats, malformations began at 0.8 times human drug exposure. These adverse effects included early embryonic deaths, abnormalities in kidneys and blood vessels, as well as irregular ossification of many bones in the skeleton and skull.[30,31] Misshapen oropharynx and/or narrowed opening into the larynx and umbilical hernia exceeded both concurrent and historical controls rates in rats; malformations of the kidneys, eyes, forelimbs, brain, major blood vessels, and heart exceeded concurrent and historical controls in rabbits.

IV. HUMAN SAFETY

The clinical safety review listed 18 safety concerns with liraglutide. The most serious are discussed below.[32]

A. Effects on the thyroid

1. Calcitonin levels

Calcitonin is a 32 amino acid polypeptide synthesized mainly in thyroid C-cells. Since C-cell tumors (the type of tumor seen in liraglutide carcinogenicity studies) secrete calcitonin at above normal levels, its accurate measurement forms an important screening tool for thyroid C-cell tumors.[33]

Because of the appearance of thyroid C-cell tumors in both sexes of rats and mice at drug-exposure levels at or below those seen in people (something not previously observed for any FDA-approved drug), the assessment of calcitonin levels became a key issue in the approval process for liraglutide. Yet, it is impossible to know what those calcitonin levels actually were in

[30] Victoza drug label. Available at http://www.victozapro.com/pdf/Victoza_ComboPI_5.24.pdf. Accessed February 16, 2012.
[31] FDA Pharmacology Review. Available on web page 2-3 at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed February 23, 2012.
[32] FDA Clinical Safety Review. Web page 151-153. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 16, 2012.
[33] FDA Clinical Safety Review. Web page 148. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed March 1, 2012.

subjects enrolled in the liraglutide clinical trials. This is because the two main pieces of information necessary for evaluating calcitonin measurements were not provided: First, there was no presentation of individual arithmetic data (as opposed to log transformation of data to produce geometric means). Second, there was no description or validation of the calcitonin assay used.

Figure 2 shows how differently data appear when plotted arithmetically (insert on the upper right) versus logarithmically (the main graph).[34] The logarithmic transformation is done when there is a skewed distribution with a few rare events. Since Novo Nordisk presented calcitonin data only as geometric means after a log transformation, we are prevented from seeing the details on those subjects with high calcitonin levels. The FDA was provided only with one data point, the maximum point after transformation, approximately 2.1 Figure 2. Thus, the details of data from subjects with high calcitonin levels from liraglutide would have been obscured with this kind of data presentation.

Figure 2. Level of 96 Cell Expressions Presented Arithmetically and Logarithmically

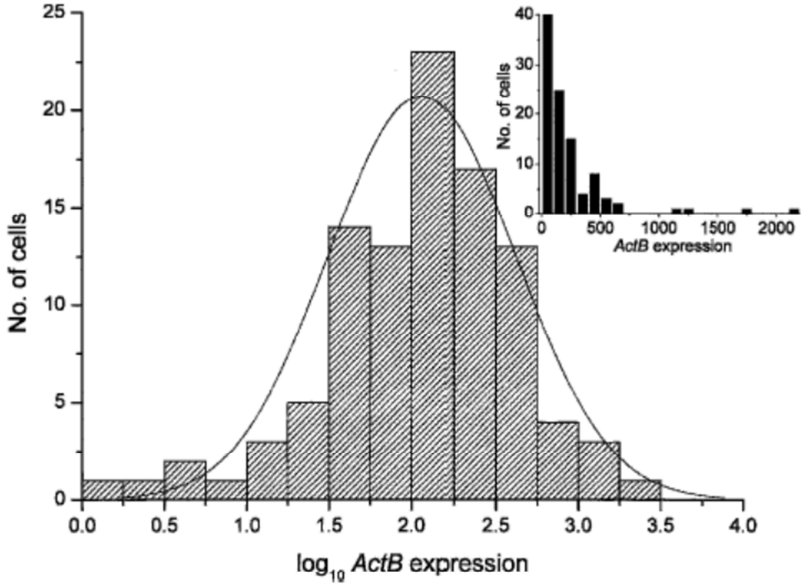

Figure 1. Histograms showing the expression levels of 96 cells expressing *ActB* in logarithmic and linear scale (*inset*). Logarithms of transcript levels are mean-centered for the two glucose concentrations. Solid line describes lognormal distribution centered on the geometric mean (2.06) of the *ActB* expression levels. *Inset* shows histogram of the expression levels in linear scale.

A study in the literature testing the same sera samples from 375 subjects with no history of thyroid disease using five different assay kits demonstrated the significant variation in measured calcitonin levels as a function of which assay was used. Figure 3 plots individual calcitonin

[34] Bengtsson M, Stahlberg A, Rorsman P, Kubista K. Gene expression profiling in single cells from the pancreatic islets of Langerhans reveals lognormal distribution of mRNA levels. Genome Res. 2005;15:1388-1392.

levels as measured by different assay kits. The "gray zone" (in the box in Figure 3) includes individuals with calcitonin levels above 10 picograms per milliliter (pg/mL), an area where patients may be at risk for having a thyroid C-cell tumor and need further evaluation. C_T on the y-axis is calcitonin level. The distribution of C_T levels showed that 4.7, 9.8, 2.5, 6.5, and 8.0% of samples tested had values greater than 10 pg/mL. In other words, using the same human blood samples, calcitonin values falling into the gray area ranged from 2.5% to 9.8% of the sample, a difference in sensitivity of almost four-fold.[35]

Since we do not know which assay Novo Nordisk used, we do not know the sensitivity of the sponsor's method. If it was an assay with low sensitivity, the results would underestimate the risk for patients.

Figure 3. Individual Calcitonin Levels as Measured by Different Assay Kits

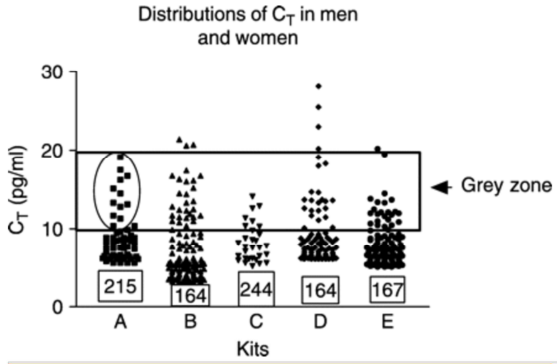

Figure 1

C_T concentration distributions established with the five assays. The numbers of undetectable C_T levels, with each assay, were noted in the rectangles near the *x*-axis.

Letters A through E are five commercially available calcitonin assay kits.

Plasma calcitonin levels were measured in the mouse carcinogenicity study of liraglutide (see Table 10)[36] but were not provided for the rat carcinogenicity study, although rats were most susceptible to the development of liraglutide-induced thyroid tumors. Unlike in the data on humans, mouse calcitonin levels were not log transformed. In general, calcitonin levels in the mice increased with increasing liraglutide dose and increasing duration of exposure. Even in the mice given the lowest dose, calcitonin levels were significantly increased (represented by underlined figures in Table 10) compared to unexposed, control mice. Satellite groups for calcitonin measurement had 17 mice per group initially, although, for some reason, samples were not available from all mice.

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[35] D'Herbomez M, Caron P, Bauters C et al. Reference range of serum calcitonin levels in humans: influence of calcitonin assays, sex, age, and cigarette smoking. Eur J Endocrinol. 2007;157:749-755.
[36] FDA Pharmacology Review. Web page 19. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed February 17, 2012.
[35a] FDA Clinical Safety Review. Web page 128. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.

Table 10. Calcitonin Levels in the Mouse Carcinogenicity Study

Plasma Calcitonin

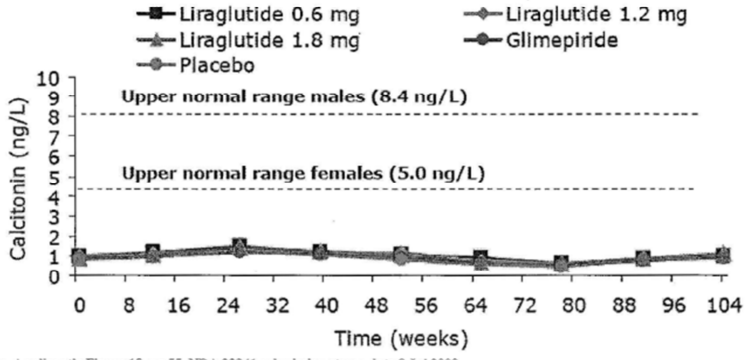
NNC 90-1170 Dose (mg/kg/day)	Males						Females					
	Week 26		Week 52		Week 104		Week 26		Week 52		Week 104	
	pg/mL	N	pg/mL	N	pg/mL	N	pg/mL	N	pg/mL	N	pg/mL	N
0	17.9	16	8.58	15	9.67	12	76	16	63.3	15	13.3	3
0.03	22.6	17	25.05	14	20.92	4	33.4	16	52.3	16	39.1	4
0.2	65.1	17	66.43	17	102.16	8	125.6	16	107.4	13	61.4	2
1	129.2	15	70.3	13	228.5	11	152.9	17	129.5	12	98.6	2
3	119	15	211.4	15	453.9	5	133.7	16	191.4	14	383.5	7

Values statistically significantly different from control are underlined.

Figure 4 is an example of calcitonin data supplied to the FDA for subjects receiving liraglutide in one liraglutide clinical trial (only geometric means provided). This data is in contrast to studies in the literature where the main interest is the proportion of individuals that exceed the normal range.[35a] We include this figure to show how lacking in information, and thus misleading, the data were that the FDA used to make its decisions.

Figure 4. Example of Calcitonin Data Supplied to the FDA for Subjects Receiving Liraglutide

Figure 7.2.9.39.2: Geometric Mean Calcitonin Values Through Two Year Extension Data, Study 1572



Yet, in spite of the use of the sponsor's inappropriate use of geometric means for presenting the data on calcitonin levels, the clinical safety reviewer was able to discover that, by weeks 26 and 28, there was a dose-dependent increase in the percent of women who had a shift in their calcitonin levels from below the lower limit of quantitation to within the range of quantitation while receiving liraglutide**.** The clinical safety reviewer concluded, "The percentage of women who exhibited this shift was numerically higher for each of the LGT [liraglutide] dose groups than for either placebo or active comparator."[37]

[37] FDA clinical review; web page 42; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed March 5, 2012.

2. Papillary thyroid cancer

Across all clinical trials presented in the new drug application (NDA) for liraglutide, through the time of the 120-day subject safety update, there were seven cases of papillary thyroid cancer requiring surgery: six were in liraglutide-treated subjects and one was in a comparator control-group subject.

Four of the six liraglutide-treated subjects were taking the highest dose, 1.8 mg. Of the six liraglutide-treated subjects who developed papillary thyroid cancer, four subjects had "elevated calcitonin" preoperatively, one had an elevated calcitonin at baseline upon study enrollment, and one did not have any calcitonin data reported. The single control subject who developed thyroid cancer had an elevated calcitonin level preoperatively. Actual calcitonin values from only two subjects were provided in the FDA clinical safety review, one taking liraglutide (19 ng/L) and the other taking comparator drugs (22 ng/L).[38]

All subjects who were diagnosed with papillary thyroid cancer had been exposed to the study drug for less than one year. All of these subjects went to surgery because of findings discovered on protocol-specified calcitonin or ultrasound screening. The papillary thyroid carcinomas were often very small: The four subjects whose information was provided had nodules less than 1 centimeter and several were about 1 millimeter in size. Three of the six liraglutide-treated subjects who had papillary thyroid cancer also had C-cell hyperplasia on pathology.[39] Information from the seven subjects is provided Table 11.

[38] FDA Clinical Safety Review. Web pages 30-34. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.
[39] FDA Clinical Safety Review. Web page 34. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.

Table 11. Papillary Thyroid Cancer Cases in Subjects Taking Liraglutide or Comparator Drugs in Preapproval Clinical Trials[40]

Table 7.1.3.3.2.2.1.2: Papillary Thyroid Cancer Cases from the Liraglutide Development Program

Study	Pt ID	Age	Gender	Tx	Exp	Outcome	Tumor Size	Comment
1334	16004	70	f	LGT 0.6	99 d	Thyroid surgery; adjuvant treatment not mentioned; longterm outcome not mentioned	T1 (<2 cm)	
1573	261006	62	f	LGT 1.2	356 d	"	1 mm	Elevated calcitonin preop; C-cell hyperplasia on path
	175008	64	m	LGT 1.8	26 d	"	1 mm	Elevated baseline calcitonin; C-cell hyperplasia on path, "may also be referred to as 'medullary carcinoma *in situ*'"
1436	506001	59	m	LGT 1.8 + GLIM	175 d	"	?	Elevated calcitonin preop
1572	221008	54	m	LGT 1.8 + MET	364 d	"	2 mm	Elevated calcitonin preop; C-cell hyperplasia on path
1574	326016	53	f	LGT 1.8 + MET + RSG	50 d	"	9 mm, 2.5 mm, 1 mm	Elevated calcitonin preop
	326008	59	m	MET + RSG	61 d[1]	"	1 mm	Elevated calcitonin preop

Source: Applicant's Table 2-23 and narratives, Module 2.7.4, beg pg 115
Abbreviations: Exp = duration of exposure to study medication prior to time cancer was noted, f = female, GLIM = glimepiride, ID = patient identification number, LGT = liraglutide, m = male, MET = metformin, Path = pathology results, preop = preoperatively, Pt = patient, RSG = rosiglitazone, Tx = study drug treatment
1 The applicant's table states that the exposure was 1 day, but the clinical safety reviewer calculates 61 days.

Across all completed clinical trials submitted with the liraglutide NDA, the rate of papillary thyroid cancer (normalized to duration of subject exposure) was three-fold higher in subjects receiving liraglutide (**2.1 per 1,000 patient years)** in comparison to control subjects receiving comparator drugs (**0.7 per 1,000 patient years)**.[41]

3. Human C-Cell hyperplasia

Across all completed clinical trials submitted with the liraglutide NDA, five cases of C-cell hyperplasia (an abnormal increase in C-cells, the cells that produce calcitonin) were reported in liraglutide-treated subjects versus one case among comparator-treated subjects, representing **1.7 cases per 1,000 patient years** versus **0.7 cases per 1,000 patient years**, a 2.4-fold increase when normalized to the duration of subject exposure. Information from the seven subjects is provided in Table 12. All cases were detected through preplanned clinical trial monitoring of calcitonin and had relatively mild preoperative calcitonin elevations.[42]

[40] FDA Clinical Safety Review. Web page 31. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.
[41] FDA Clinical Safety Review. Web page 30. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.
[42] FDA Clinical Safety Review. Web pages 35 and 37. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.

Table 12. C-cell Hyperplasia Diagnosed in Clinical Trials of Liraglutide

Table 7.1.3.3.2.3: C-Cell Hyperplasia Case Features, All Cases Reported as of 26 Jun 2009						
ID and Gender	**Tx**	**Exp (days)**	**BL Static Calcitonin[1] (ng/L)**	**Preop Static Calcitonin[1] (ng/L)**	**Preop Stim Calcitonin Pk[2] (ng/L)**	**Path**
228002 m	LGT 0.6	190	21.5	15	142	Diffuse CCH
261006 f	LGT 1.2	484	1.7	4.6	94	Diffuse CCH
221008 m	LGT 1.8	363	15.1	22.3	508	Diffuse CCH
651009 m	LGT 1.2	194	11.6	16.4		Focal CCH
175008 m	LGT 1.8	28	22.3	29.4	?	"MTC *in situ*"
224012 m	MET + GLIM	370	"normal"	12.1	"abnl"	"MTC *in situ*"
1 ULN (ng/L): M = 8.4; F = 5 **2 ULN (ng/L): M = 130; F = 90**						

* **Tx = treatment; LGT = liraglutide; MET = metformin; glim = glimepiride**

4. Medullary thyroid carcinoma

Medullary thyroid carcinoma is a form of thyroid cancer that originates in the C-cells. Across all completed clinical trials submitted with the liraglutide NDA, medullary thyroid carcinoma was diagnosed in a single comparator-treated subject, who evidently had this condition prior to enrollment: the subject's baseline calcitonin was greater than 1,000 ng/L (the geometric mean in the five major trials was about 1 ng/L).[43] It is troubling that such a person was allowed to enroll in a trial testing liraglutide. One liraglutide-treated subject developed medullary thyroid carcinoma *in situ*.[44]

5. All types of thyroid neoplasm adverse events

Across all completed clinical trials submitted with the liraglutide NDA, there were a total of 19 serious and nonserious thyroid neoplasms for liraglutide versus five for comparator-treated subjects, yielding a rate for liraglutide of **9.8 cases per 1,000 patient years versus 4.4 cases per 1,000 patient years** for comparators, a more than two-fold increase (Table 13).[45]

[43] FDA Clinical Safety Review. web page 30. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.
[44] FDA Clinical Safety Review Web page 36. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.
[45] FDA briefing document for the April 2, 2009 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. Web page 109. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM148645.pdf. Accessed February 17, 2012.

Table 13. Thyroid Adverse Events in Clinical Trials of Liraglutide

Table III.B.2.e: Thyroid Adverse Events, Safety Analysis Set at Time of NDA Submission							
System Organ Class	Preferred Term	LGT N=4211 PY=2241			Non-LGT N=2272 PY=1139		
		n	%	Rate per 1000 PY	n	%	Rate per 1000 PY
	Thyroxine decreased	1	<0.1	0.4	0	0	0
	Blood TSH decreased	0	0	0	1	<0.1	0.9
Endocrine disorders	Any thyroid term	21	0.5	11.6	7	0.3	6.1
	Goitre	15	0.4	7.1	1	<0.1	0.9
	Hypothyroidism	3	0.1	1.3	4	0.2	3.5
	Hyperthyroidism	2	<0.1	0.9	0	0	0
	Thyroid cyst	2	<0.1	0.9	0	0	0
	Thyroid disorder	2	<0.1	0.9	0	0	0
	Autoimmune thyroiditis	1	<0.1	0.4	2	0.1	1.8
Neoplasms	Any thyroid term	19	0.5	9.8	5	0.2	4.4
	Thyroid neoplasm	15	0.4	7.1	4	0.2	3.5
	Papillary thyroid cancer	4	0.1	1.8	1	<0.1	0.9
	Benign neoplasm of thyroid gland	1	<0.1	0.4	0	0	0
	Parathyroid tumor benign	1	<0.1	0.4	0	0	0
Source: Applicant's Table 2-19, pg 110, ISS Abbreviations: LGT = liraglutide, PY = patient-years, TSH = thyroid stimulating hormone							

6. Major Adverse Cardiovascular Events (MACE)

The risk of MACE was one of the two serious safety issues that Dr. Karen Murry Mahoney, the FDA clinical safety reviewer, discussed in her NDA review (the other being thyroid tumors).[46] MACE was also discussed at the April 2, 2009, meeting of the EMDAC.[47] Dr. Mahoney outlined the reasons why it was not possible to obtain valid data for MACE: The clinical studies of liraglutide had not been designed to be combined for meta-analysis (trials varied in duration, blinding, and open-label extensions) and were done without prospectively planned adjudication of cardiovascular events.

Furthermore, subjects were specifically excluded from clinical trials of liraglutide if they had "significant cardiovascular conditions" (New York Heart Association class III and IV).[48] As a result, there were few MACE on which to base an analysis.

Both cardiologist members of and the biostatistician member on the EMDAC agreed with the concerns raised by Dr. Mahoney, voting that there was not enough data to rule out an unacceptable excess cardiovascular risk of liraglutide relative to comparator drugs.[49]

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[46] FDA Clinical Safety Review; web page 147; Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 23, 2012.

[47] Transcript for the April 2, 2009 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for liraglutide. Web page 88. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM151176.pdf. Accessed February 17, 2012.

[48] FDA Clinical Safety Review; web page 54; Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 23, 2012.

[49] FDA Clinical Safety Review. Web page 137-138. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 23, 2012.

The biostatistician stated, "I don't think that they have ruled out the possibility of an unacceptable excess cardiovascular risk. I am also troubled by other things like the fact that the relative risk versus placebo was greater than the relative risk versus comparators. So taking that into consideration together with the issue of adjudication and everything else, to me it didn't rule out unacceptable excess cardiovascular risk."[50]

7. GI effects

GI adverse events occurred in a large percent of subjects enrolled in trials of liraglutide. For example, in the 52-week trial comparing monotherapy with liraglutide to the older diabetes drug glimepiride, subjects receiving liraglutide had higher rates of nausea (three times higher than subjects receiving the comparator drug glimepiride), vomiting (three times higher), diarrhea (almost two times higher), and constipation (two times higher) (Table 14). The increased adverse event rates in one of the 26-week trials were similar (Table 15).

Table 14. Adverse Events Reported in ≥5% of Subjects (52-Week Study #1573)[51]

Adverse Event Term	Victoza (%)	Glimepiride (%)	Ratio Victoza/glimepiride
Nausea	28	8.5	3.3
Diarrhea	17	8.9	1.9
Vomiting	11	3.6	3.1
Constipation	9.9	4.8	2.1

Table 15. Adverse Events Reported in ≥5% of Subjects (26 Week Study #1574)[52]

Adverse Event Term	Victoza +metformin +rosiglitazone (%)	Placebo +metformin +rosiglitazone (%)	Ratio Victoza/placebo
Nausea	35	8.6	4.1
Diarrhea	14	6.3	2.2
Vomiting	12	2.9	4.1
Decreased appetite	9.3	1.1	8.5
Constipation	5.1	1.1	4.6

8. Pancreatitis

Across all completed clinical trials submitted with the liraglutide NDA, there were a total of nine cases of acute pancreatitis, with eight cases in liraglutide-treated subjects (one of which was fatal) and one case among comparator-treated subjects. Adjusted for duration of exposure to study drugs, the rate of acute pancreatitis was **2.2 cases per 1,000 patient years in liraglutide-**

[50] Transcript for the April 2, 2009 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for liraglutide. Web page 195. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM151176.pdf. Accessed February 17, 2012.

[51] Novo Nordisk Inc. Victoza drug label. Web page 3. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 17, 2012.

[52] Novo Nordisk Inc. Victoza drug label. Web page 3. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 17, 2012.

treated subjects versus **0.6 cases per 1,000 patient years in control subjects**, a 3.7-fold increase.[53] The clinical safety reviewer stated that "[p]ancreatitis may be a class effect for GLP-1 analogues, given recent findings with exenatide" and felt that labeling regarding the risk of pancreatitis, both wording and placement, should be the same as those for exenatide, the only other FDA-approved GLP-1 agonist, which they are not.[54] Such a dramatic safety signal for acute pancreatitis is unusual during the clinical development program for an NDA.

9. Serious adverse events of neoplasms

Across all completed clinical trials submitted with the liraglutide NDA, after the inclusion of data from the 120-day subject-safety update, the clinical reviewer found a rate for all serious neoplastic events of **12.3 per 1,000 patient years in liraglutide-treated subjects versus 8.1 events per 1,000 patient years in control subjects** with no particular cancer-cell type predominating.[55]

A possible explanation for this difference in neoplastic events was thought to lie in epidemiologic data that suggested an association between higher insulin levels (which are increased with liraglutide) and increased malignancy risk.[56] Another possible mechanism that remains to be explored is whether GLP-1 shares some of the potential shown by the related glucagon-like peptide-2 (GLP-2) to transform preneoplastic growths to tumors (it does not appear that GLP-1 has been studied in this regard). GLP-2 is co-secreted from the intestinal enteroendocrine cells (along with GLP-1) and has been shown to promote the growth of mucosal neoplasms in the colons of mice induced with a carcinogen and treated with stable GLP-2 analogues.[57] Exposure of human colon cancer cell lines to GLP-2 plus an inhibitor of the enzyme that degrades GLP-2 also resulted in increased cell proliferation.[58]

10. Serious hypoglycemic events

All nine cases of serious hypoglycemic events, defined as an event requiring the assistance of another person for treatment, occurred in liraglutide-treated subjects across the five major phase 3 clinical trials submitted with the liraglutide NDA. In six of the nine cases, patients were also taking a sulfonylurea drug and, in two of the nine cases, metformin.[59] There were no cases of serious hypoglycemic events in the comparator or control groups during clinical trials.

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[53] Novo Nordisk Inc. Victoza drug label. Web page 2. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 17, 2012.

[54]FDA Clinical Safety Review. Web page 152. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 12, 2012.

[55] FDA Clinical Safety Review. Web page 119. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2 .pdf. Accessed February 12, 2012.

[56] Taubes G. Unraveling the obesity-cancer connection. Science 2012;335:28-32.

[57] Thulesen J, Hartmann B, Hare KJ et al. Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice. Gut 2004;53:1145-1150.

[58] Masur K, Schwartz F, Entschladen F, et al. DPPIV inhibitors extend GLP-2 mediated tumour promoting effects on intestinal cancer cells. Regul Pept. 2006;137:147-155.

[59] FDA Clinical Safety Review. Web page 152. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 12, 2012.

11. Injection-site reactions[60]
Across all completed clinical trials submitted with the liraglutide NDA, injection-site reactions occurred more frequently among liraglutide-treated subjects than among placebo- or insulin-treated subjects and showed a dose dependency. All of the withdrawals for this adverse effect occurred in liraglutide-treated subjects. In studies with monkeys, some of these reactions were irreversible and were associated with peripheral eosinophilia.

12. Increased heart rate
Across all completed clinical trials submitted with the liraglutide NDA, "[l]iraglutide was associated with a small but statistically significant increase in heart rate in the five major Phase 3 trials"[61] The FDA reviewer noted that, in liraglutide-treated subjects compared to control subjects, "[a]dverse events related to heart rate ("heart rate increased," tachycardia, supraventricular tachycardia, sinus tachycardia or tachycardia paroxysmal), occurred slightly numerically more frequently among liraglutide-treated patients than among comparator-treated patients."[62]

A higher mean heart rate was also observed in subjects taking exenatide.[63]

Studies in rats suggest these cardiovascular effects of GLP-1 agonists may be mediated by effects on the hypothalamo-pituitary-adrenocortical axis and the autonomic nervous system.[64]

13. Renal impairment
In May 2011, as a result of post-marketing reports, the FDA required the addition of a new warning to the label for liraglutide, stating that health care professionals and subjects need to be alert to signs of "acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis." Most of these cases were in patients who had experienced nausea, vomiting, diarrhea, or dehydration.[65] Since these are common adverse events in patients taking liraglutide, it may make it difficult to promptly identify the cause (see sub-subsection 7, "GI events").

14. Pregnancy
Of the five women who became pregnant while taking liraglutide during the NDA clinical trials, two terminated their pregnancies, one had a miscarriage, and two had healthy babies. One woman took 3.0 mg/day, three took 1.8 mg/day, and one took 1.2 mg/day. Two women on comparator drugs (one on metformin and one on rosiglitazone plus glimepiride) had

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[60] FDA Clinical Safety Review. Web page 153. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 12, 2012.
[61] FDA Clinical Safety Review. Web page 25. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed April 2, 2012.
[62] FDA Clinical Safety Review. Web page 155. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 12, 2012.
[63] Diamant M, Van Gaal L, Stranks S, et al. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet. 2010;375:2234-2243.
[64] Yamamoto H, Lee CE, Marcus JN, et al. Glucagon-like peptide-1 receptor stimulation increases blood pressure and heart rate and activates autonomic regulatory neurons. J Clin Invest. 2002;110:43-52.
[65] Novo Nordisk Inc. Victoza drug label. Web page 2. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 12, 2012.

miscarriages.[66] This sample is too small to draw any conclusions as to liraglutide's effect on neonatal health, but the sharply increased incidence of malformations in rats and rabbits in preclinical studies at exposures similar to those in people, provides a reason to be very cautious.

15. Hypersensitivity reactions
Analysis was provided by a consultant from the FDA's Division of Pulmonary, Allergy, and Rheumatology Products and is discussed on page 33 (see subsection F, "Hypersensitivity reactions").

V. RECOMMENDATIONS OF THE FDA STAFF (AGAINST APPROVAL)

All three of the safety reviewers (clinical and pharmacology/toxicology), as well as the clinical safety reviewer, thought that liraglutide had too many safety issues to warrant approval.

A. Pharmacology/toxicology primary review (Dr. Anthony Parola)

The recommendation was "*Not approvable* [emphasis added]."[67]

This reviewer's conclusion of "not approvable" was related to unresolved toxicology issues, most importantly the unknown relevance to humans of the liraglutide-induced thyroid C-cell tumors seen in rats and mice at clinically relevant exposures. The reviewer was also concerned by the use of lower concentrations of liraglutide in nonclinical formulations in repeat-dose studies that might have underestimated exposure.

B. Pharmacology supervisor memorandum (Dr. Karen Davis-Bruno)

Dr. Parola's supervisor, Dr. Davis-Bruno, stated that, "Dr. Parola's Pharmacology/Toxicology review of the available nonclinical data recommends not approving this marketing application. *I agree with his recommendation* based on the clear drug-related carcinogenicity signal observed in rodent life-time bioassays at relevant therapeutic exposures [emphasis added]."[68]

C. Associate director for pharmacology and toxicology memorandum (Dr. Paul Brown)

At the next higher review level, Dr. Brown stated, "*I agree that the tumor findings are significant enough to warrant further evaluation of the risk* [emphasis added]."[69]

He continued, "The concern about the tumorigenic potential of liraglutide would be diminished if it was clearly demonstrated that it produced tumors by a mechanism that was not relevant to humans." However, he noted that "[t]he executive carcinogenicity assessment committee agreed that the applicant had not shown convincingly that the tumor findings were irrelevant to humans." And "it appears possible that at least a segment of the population could be at increased risk." Furthermore, if approved, "it would be challenging to incorporate as a part of routine

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[66] FDA Clinical Safety Review. Web page 103. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.
[67] FDA Pharmacology Review. Web page 4. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed February 17, 2012.
[68] Davis-Bruno K. Memorandum from Pharmacology Supervisor to NDA 22-341. July 13, 2009. Web page 7. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 17, 2012.
[69] Tertiary Pharmacology/Toxicology Review. Web pages 3-4. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. Accessed February 17, 2012.

therapy, adequate and clinically acceptable monitoring for preneoplastic thyroid effects and thyroid tumors." [There is no such monitoring recommended in the drug label.]

D. Clinical safety review (Dr. Mahoney)
"The clinical safety reviewer *does not recommend approval* of liraglutide at this time, for two reasons [emphasis added]:

- "A strong signal in animals of C-cell tumors of the thyroid gland, with inadequate duration of controlled study in humans to adequately assess the human risk, and
- "Inadequate data to assess the risk of major adverse cardiovascular events in humans."[70]

She continued her argument against approval: "In the United States, there are already 11 classes of drugs approved for glycemic control in type 2 diabetes, and one other in this class [exenatide]. The need for new therapies for type 2 diabetes is not so urgent that one must tolerate a significant degree of uncertainty regarding serious risk concerns."

VI. RECOMMENDATIONS OF THE FDA STAFF (FOR APPROVAL)

A. Comments of the director of the Office of Drug Evaluation II (Dr. Curtis Rosebraugh)[71]

1. Cardiovascular events
Dr. Rosebraugh noted that, in spite of the small numbers of events, the lack of pre-specified definitions or prospective adjudication of major cardiovascular end points, he was reassured from the analysis of what data was available that liraglutide "will not have a negative cardiovascular impact."[72]

Dr. Rosebraugh based his conclusions, in part, on the vote of the advisory committee panel, which thought that there were enough cardiovascular safety data to allow marketing, even though both cardiologists on the committee (Dr. John Teerlink and Dr. Marvin Konstam) and the biostatistician on the committee (Dr. Michael Proschan) disagreed.[73] Dr. Rosebraugh felt that, "the application provides the same level of confidence regarding cardiovascular safety as that provided by the saxagliptin analysis (which the advisory committee had discussed the day before)."[74]

Dr. Rosebraugh's opinion contradicted that of the FDA's clinical safety reviewer, Dr. Mahoney, who had noted that the studies had not been designed to be combined for meta-analysis (trials

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[70] FDA Clinical Safety Review. Web page 146. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 17, 2012.
[71] FDA Summary Review. Web pages 2-19. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed February 17, 2012.
[72] FDA Summary Review. Web page 13. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed February 17, 2012.
[73] FDA Clinical Safety Review. Web page 137-138. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 23, 2012.
[74] FDA Summary Review. Web page 13. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.

had varied in duration, blinding, and open-label extensions), the studies were done without prospectively designed adjudication of cardiovascular events, and patients were specifically excluded from clinical trials if they had "significant cardiovascular conditions" (New York Heart Association class III and IV).

2. Thyroid cancer

a. Calcitonin levels: Dr. Rosebraugh was seemingly comforted by the fact that mean values of calcitonin did not change over time in subjects receiving liraglutide for any doses and that these values were below the upper range of normal for both sexes. Although liraglutide "has demonstrated dose-related carcinogenic potential in both genders of rats and mice ... at clinically relevant exposures," he was "reassured that the use of liraglutide [in subjects] was not associated with increase[d] levels of serum calcitonin in over 2 years of therapy," based on pooled geometric mean data.[75] (See subsection 1, "Calcitonin levels," under section IV, "Human Safety," for a critique on the usefulness of Novo Nordisk's geometric mean data in humans.)

He objected to routine screening of calcitonin or ultrasonography in patients who would be treated with liraglutide since it might lead to unnecessary thyroidectomies (even though monitoring was the only way that thyroid tumors were discovered in the clinical trials).[76] He also disregarded the calcitonin level shift upward with increased dose that Dr. Mahoney presented, as well as the almost four-fold excess of thyroid tumors in liraglutide-treated subjects.

As for further trials, he felt that neither preclinical nor clinical trials could answer the question as to whether liraglutide causes medullary thyroid tumors because these tumors are so rare and trials would have to be enormous and/or run for a long time to answer the question[77] (unless liraglutide changed that frequency of occurrence of such tumors, which is what happened in rats and mice).

b. Thyroid carcinomas: Dr. Rosebraugh also took comfort from knowing that the rodent malignant tumors were "very few in number," in spite of the fact that, for a very rare tumor, the presence of a few tumors is an important signal.[78] This is especially true in studies where the power to detect is low (in carcinogenicity studies, a group of 50 animals represent the human population).

He stated, quite incorrectly, that "even the rodent models did not have carcinomas above baseline rates at doses approximating human exposures,"[79] when, in fact, male rats had statistically increased levels of thyroid carcinomas at 0.5 times the expected human exposure and female rats

[75] FDA Summary Review. Web page 7. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[76] FDA Summary Review. Web page 17. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 5, 2012.
[77] FDA Summary Review. Web page 12. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[78] FDA Summary Review. Web page 15. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[79] FDA Summary Review. Web page 12. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.

had statistically increased levels of thyroid carcinomas at twice the expected human exposure, rates higher than both concurrent and historical controls (Table 6).

c. Monkey study: Dr. Rosebraugh found the lack of thyroid C-cell lesions in monkeys reassuring[80] — even though monkeys were treated for only 5% of their lifespan (versus the rodent studies, which involved their entire lifespan) and numbers tested were very small (40 monkeys versus 400 rats and mice). Thus, since the power to detect cancer in the monkey toxicity studies was very much lower than the rodent studies negative response is not meaningful.

Another argument Dr. Rosebraugh used to justify his recommendation was that the FDA has previously approved a drug that caused cancer in carcinogenicity studies (pioglitazone: bladder cancer), a drug that "continues to receive support by practicing physicians." This "support" may decrease because FDA has recently (June 15, 2011, and August 4, 2011) had to issue warnings about bladder cancer in patients treated with pioglitazone and has changed the labeling for all drugs containing pioglitazone.[81,82]

3. Pancreatitis

Dr. Rosebraugh noted that pancreatitis may be a class effect of incretin drugs. However, he stated that, even if one assumes that this class of drugs does cause pancreatitis, the FDA would not remove them from the market but instead would "encourage awareness and early diagnosis." He continued, "I do not think that we have evidence that liraglutide is any worse [an] offender in this regard than the other agents."[83]

However, liraglutide, unlike exenatide, the other FDA-approved drug in this class, had an excess of cases of pancreatitis during controlled clinical trials, and the FDA has continued to receive numerous pancreatitis adverse reaction reports since the drug has been on the market. As a consequence, the FDA has felt it necessary to issue a safety alert about liraglutide.[84]

4. Risk/benefit

Finally, Dr. Rosebraugh listed the benefits of liraglutide as less hypoglycemia (even though it was only the liraglutide-treated subjects that had cases of serious hypoglycemia), weight loss (versus weight gain with some other diabetes drugs), comparable or even increased HbA1c reduction (the surrogate end point) in comparison to results with other diabetes drugs, as well as

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[80] FDA Summary Review. Web page 26. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.

[81] Food and Drug Administration. FDA drug safety communication: updated drug labels for pioglitazone-containing medicines. August 4, 2011. Available at http://www.fda.gov/Drugs/DrugSafety/ucm266555.htm. Accessed February 17, 2012.

[82] Food and Drug Administration. FDA drug safety communication: update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. June 15, 2011. Available at http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm. Accessed February 17, 2012.

[83] FDA Summary Review. Web page 17. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.

[84] Food and Drug Administration. Safety alert: Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis. June 13, 2011. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm. Accessed February 17, 2012.

the once-daily dosing schedule. He predicted that dosing schedules will improve to be even more "user-friendly," to weekly or even monthly dosing.[85]

His final comment was that, "[w]hile many sponsors may responsibly introduce a drug into marketing, theirs is a profit-based business and the pressures to generate revenue are strong. Also, with most classes of drugs, there are similar drugs in development from competitors which places even more pressure to generate profit before there is more competition," a comment that one would expect from Novo Nordisk or Wall Street, not the FDA.[86] To justify the FDA's decision in light of all of the safety problems that had been identified, Dr. Rosebraugh added, "Limitations placed on labeling will help in assuring prudence with a drug that has many unknowns and may help to motivate the sponsor to complete animal studies with the goal of liberalizing labeling."[87]

Finally, he said, "I recommend approval."[88]

B. Comments of the director of the Division of Metabolic and Endocrine Drug Products (Dr. Mary Parks)[89]

1. Cardiovascular risks

Dr. Parks pointed out that the guidance for cardiovascular studies is just that, guidance and not a regulatory requirement. "In my opinion, this NDA has sufficiently demonstrated an acceptable CV [cardiovascular] risk profile premarketing."[90]

2. C-cell tumor risk

Dr. Parks' opinion was that calcitonin analyses were exploratory and clinical relevance was "highly questionable." She felt that the GI symptoms could have influenced the investigators to suspect that these subjects were taking liraglutide and resulted in more monitoring of them since investigators would be more concerned that someone taking liraglutide was at more risk for C-cell tumors.[91]

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[85] FDA Summary Review. Web page 16. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[86] FDA Summary Review. Web page 17. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[87] FDA Summary Review. Web page 18. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[88] FDA Summary Review. Web page 18. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012.
[89] FDA Summary Review. Web pages 20-65. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed February 17, 2012.
[90] FDA Summary Review. Web page 47. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012
[91] FDA Summary Review. Web page 48-50. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012

3. Pancreatitis

Since there was an imbalance in the number of cases of pancreatitis in the liraglutide-treated subjects, she recommended inclusion of a warning about pancreatitis in the labeling under the "Warnings and Precautions" section.[92]

4. Conclusions

Dr. Parks had serious concerns as to whether the adverse effects of this drug would be understood by health care providers and patients. She wanted a Medication Guide as well as post-marketing studies on cardiovascular safety, pediatric studies, and a registry for medullary thyroid tumors. She concluded, "I believe liraglutide should be approved with limitations on its use [i.e., use only after other drugs were shown not to work] and labeling which would circumscribe marketing and promotional practices until completion of several studies/trials under FDAAA [Food and Drug Administration Amendments Act]."[93]

VII. PUBLIC CITIZEN DISCUSSION OF SAFETY ISSUES

There are at least six serious safety issues, any one of which should have precluded approval of liraglutide. The most often cited were all, except renal toxicity, noted preapproval:

- Thyroid carcinogenicity and other thyroid toxicity
- Inadequately evaluated risk for MACE
- Acute pancreatitis
- Other serious neoplastic events, including pancreatic cancer
- Renal toxicity
- Hypersensitivity reactions

A. Thyroid toxicity

1. Data from the NDA

Liraglutide is a drug that, in both mice and rats, had a stronger thyroid cancer signal than ever seen before for any drug (both approved and in the pipeline), including the other GLP-1 agonist, exenatide. Yet the FDA was willing to overrule the conclusions of its own pharmacologists and medical safety officer and disregard this information, even when combined with a clinical signal of increased risk in subjects in relatively short-term studies.

It is troubling that when animal carcinogenicity studies are positive, the FDA and sponsors do their utmost to find reasons why the results do not apply to humans, yet the whole point of doing carcinogenicity studies is to pick up possible warning signals of cancer-related safety issues prior to human exposure. There is almost never enough information as to drug biotransformation and mechanism of action to rule out tumor formation in people if the animal studies are positive.

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[92] FDA Summary Review. Web page 51. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 1, 2012

[93] FDA Summary Review. Web page 62. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf. Accessed March 5, 2012

To the question, "Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?" the FDA's EMDAC had one member vote "yes" and 12 vote "no," with both thyroid cancer experts voting "no."

2. Data from the literature

There is strong evidence from the literature for GLP-1 binding to human thyroid tissue. Körner et al found radioactive GLP-1 binding to both human medullary thyroid carcinomas as well as normal thyroid.[94] They also found GLP-1Rs in numerous other types of tumors, including pheochromocytomas, central nervous system tumors, embryonic tumors, and ovarian adenocarcinomas. Although they reported only 1/18 normal thyroids had GLP-1Rs, there are unknown technological questions as to how long and at what temperature tissue had been stored or how long GLP-1Rs can be frozen and still retain receptor activity.

Gier et al also found radioactive GLP-1 binding to neoplastic, hyperplastic, and normal human tissue.[95] They found that "[c]oincident immunoreactivity for calcitonin and GLP-1 receptor was consistently observed in both medullary thyroid carcinoma and C cell hyperplasia." Interestingly, GLP-1R immunoreactivity was also detected in papillary thyroid carcinoma as well as in normal human thyroid tissue (five of 15 specimens). There are technological issues here as well, since tissues studied had been stored from 2002 to 2010.

A third study by Waser et al used thyroid tissue from rats, mice, and humans (both normal thyroid and thyroid carcinomas). Although these researchers found a higher GLP-1R expression in rodent C-cell lesions than in human C-cell lesions, they concluded, "Our data, nevertheless, suggest that at present time, caution, namely thyroid monitoring, should be necessary in human trials with long-acting GLP-1 analogs." They further concluded that "[t]he presence of incretin receptors in thyroid C cell lesions suggests that this organ should be monitored before and during incretin-based therapy of diabetes."[96]

A study analyzing the AERS database found that the reporting rate for thyroid cancer in patients treated with exenatide was increased 4.7-fold compared to the rate with other therapies for diabetes.[97]

3. FDA warnings

The FDA Liraglutide Cross-Discipline Team leader had stated that "patients in all treatment arms [in the liraglutide clinical trials] underwent routine calcitonin measurements."[98] As a result, "almost all of these cancers ... were discovered at surgery that was prompted by routine protocol-

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[94] Körner M, Stöckli M, Waser B, Reubi JC. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. J Nucl Med. 2007;48:736-743.

[95] Gier B, Butler PC, Lai CK et al. Glucagon like peptide-1 receptor expression in the human thyroid gland. J Clin Endocrinol Metab. 2012;97:1-11.

[96] Waser B, Beetschen K, Pellegata NS, Reubi JC. Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: relevance for incretin-based therapy. Neuroendocrinol 2011;94:291-301

[97] Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterol. 2011;141:150-156.

[98] FDA Cross DisciplineTeam Leader Review. Web page 44. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000crossr.pdf. Accessed February 17, 2012.

specified calcitonin or ultrasound screening."[99] Yet liraglutide was approved with no requirement for health professionals to monitor calcitonin. In June 2011, the FDA issued an alert and Novo Nordisk issued a "Dear Healthcare Professional" letter warning of the risk of C-cell tumors in patients using liraglutide.[100] Still, there is nothing in the FDA-approved drug label regarding the monitoring of calcitonin levels in patients treated with this drug.

4. Data generated by Public Citizen's Health Research Group

We found 26 cases of thyroid cancer associated with liraglutide treatment by analyzing the FDA's AERS database from February 2010 through September 2011. We used MedDRA terms and found for "thyroid cancer" (n=10), "thyroid neoplasm" (n=12), "thyroid adenoma" (n=1), and "thyroid cancer metastatic" (n=3). Using a similar search, we found no thyroid cancers reported to the FDA for the diabetes drugs nateglinide, repaglinide, glipizide, or sitagliptin. There were two cases reported for rosiglitazone (thyroid adenoma and thyroid neoplasm), but twenty for exenatide, the other FDA-approved GLP-1 agonist. Thus, it appears that the two FDA-approved GLP-1 agonists (liraglutide and exenatide) share the property of increasing thyroid cancer risk.

B. MACE

To the question of whether there was "appropriate evidence of cardiovascular safety" to rule out unacceptable excess cardiovascular risk relative to comparators, the two cardiologists and the biostatistician on the EMDAC voted "no."[101] The FDA clinical safety reviewer agreed. Thus, there remains the possibility that liraglutide, like certain other diabetes medications (e.g., rosiglitazone and pioglitazone), could increase major cardiovascular adverse events to which diabetics are already at increased risk.

C. Pancreatitis and Pancreatic Cancer

1. Pancreatitis

a. Data from the NDA: There was a 3.7-fold increased risk of pancreatitis in subjects taking liraglutide compared to the risk in those using comparator drugs during the randomized clinical trials of liraglutide (Table 15). Toxicity to the pancreas was also seen in preclinical studies in rats, mice, and monkeys (focal inflammation and increased mass).

b. Data from the literature:

1) **Animal:** An experiment in a rat model of type 2 diabetes showed that drugs acting via GLP-1 caused damage to the exocrine pancreatic tissue, characterized

[99] FDA Clinical Safety Review. Web page 151. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 17, 2012.
[100] Novo Nordisk Inc. Dear health care professional letter: potential risks of thyroid C-cell tumors and acute pancreatitis associated with Victoza. Available at http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM258828.pdf. Accessed February 17, 2012.
[101] FDA Clinical Safety Review. Web page 137. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 17, 2012.

by marked ductal metaplasia and severe hemorrhagic pancreatitis.[102] Ductal proliferation and metaplasia are also components of pancreatitis in humans. Since ductal turnover is dependent on hyperglycemia, these effects would likely have been missed in the nondiabetic rodent models used in the NDA animal studies of liraglutide and would have provided falsely comforting results.

2) **Human:** What appears to be the first reported case of pancreatitis is that of a 60-year-old woman whose symptoms occurred 23 days after beginning liraglutide and resolved with discontinuation of the drug.[103] A second case concerns a 53-year-old man who developed sudden, severe abdominal pain with elevated serum amylase and lipase two months after increasing his liraglutide dose from 0.6 mg/day to 1.2 mg/day. Acute pancreatitis was diagnosed radiographically, liraglutide was discontinued, and the patient fully recovered.[104]

   Elashoff et al, using the FDA's AERS database, found "pancreatitis more than six-fold more likely to be reported in association with sitagliptin or exenatide than other drugs for type 2 diabetes" (both work through the GLP-1 receptor, as does liraglutide).[105] The rate of pancreatitis for exenatide itself was increased more than 10-fold compared to the rate for control diabetes drugs. Unsurprisingly, a published case of acute necrotizing pancreatitis has been reported in a patient taking both sitagliptin and exenatide.[106]

   There are other cases reported in the literature of pancreatitis with other drugs that work through the GLP-1 pathway: exenatide,[107] as well as two DPP-4 inhibitors (drugs that work through the GLP-1 system by blocking their breakdown) — vildagliptin[108] and sitagliptin. Diagnosis was made through the use of commuted tomography scans, elevated levels of lipase and amylase, and the presence of abdominal pain coupled with the recent introduction of the offending drug. Alcohol and gallbladder were ruled out as causative agents.

c. Data generated by Public Citizen: We found 200 cases of acute pancreatitis reported to the FDA from February 2010 through September 31, 2011. These cases were derived from the FDA's AERS database using the specific search term "pancreatitis acute" and primary suspect drug "Victoza" or "liraglutide."

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[102] Matveyenko AV, Dry S, Cox HI, et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes. Diabetes. 2009;58:1604-1615.
[103] Lee PH, Stockton MD, and Franks AS. Acute pancreatitis associated with liraglutide. Ann Pharmacother. 2011;45:e22.
[104] Knezevich E, Crnic T, Kershaw S, Drincic A. Liraglutide-associated acute pancreatitis. Am J Health Syst Pharm 2012;69:386-389.
[105] Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterol. 2011;141:150-156.
[106] Iyer SN, Drake AJ, West RL et al. A case report of acute necrotizing pancreatitis associated with a combination treatment of sitagliptin and exenatide. Endocr Pract. 2011;Nov 8:1-13.
[107] Ayoub WA, Kumar AK, Naguib HS, Taylor HC. Exenatide-induced acute pancreatitis. Endocr Pract. 2010;16:80-83.
[108] Girgis CM, Champion BL. Vildagliptin-induced acute pancreatitis. Endocr Pract. 2011;17:e48-e50.

d. Liraglutide drug label: The "Warnings and Precautions" section of the FDA-approved label for liraglutide states only that "[i]n clinical trials, there were more cases of pancreatitis among Victoza-treated patients than among comparator-treated patients. If pancreatitis is suspected, Victoza and other potentially suspect drugs should be discontinued. Victoza should not be restarted if pancreatitis is confirmed. Use with caution in patients with a history of pancreatitis."[109] This warning fails to convey the seriousness of this adverse event.

e. MedWatch warning: On June 13, 2011, the FDA issued a warning to health care professionals to be alert to the danger of acute pancreatitis.[110]

f. Comparisons to exenatide, the other approved GLP-1 agonist: Unlike the case with liraglutide, there were no cases of pancreatitis reported in the clinical trials of Byetta, but based on post-marketing reports, the "Warnings and Precautions" section of the label now states the following:

> **Based on post marketing data BYETTA has been associated with acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. After initiation of BYETTA, and after dose increases, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, BYETTA should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, BYETTA should not be restarted. Consider antidiabetic therapies other than BYETTA in patients with a history of pancreatitis** [emphasis in original]. [111]

In 2007, the FDA warned of receiving 30 reports of post-marketing cases of acute pancreatitis with Byetta, 21 involving patients who had to be hospitalized. A second warning was issued in 2008 concerning six additional patients hospitalized for hemorrhagic or necrotizing pancreatitis, two of whom died.[112]

2. Pancreatic cancer

Elashoff et al, using the FDA's AERS database, found a 2.9-fold increase in the reported rate of pancreatic cancer in patients taking exenatide. This increase was in comparison with four other

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[109] Novo Nordisk Inc. Victoza drug label. Web page 1. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 17, 2012.

[110] Food and Drug Administration. Safety alert: Victoza (liraglutide [rDNA origin]) Injection: REMS - Risk of Thyroid C-cell Tumors, Acute Pancreatitis. June 13, 2011. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm. Accessed February 17, 2012.

[111] Amylin Pharmaceuticals, Inc. Byetta drug label. Web page 3. Available at http://pi.lilly.com/us/byetta-pi.pdf. Accessed February 17, 2012.

[112] Food and Drug Administration. Safety alert: Byetta (exenatide). October 2007; updated August 18, 2008. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150839.htm. Accessed February 14, 2012.

older drugs for diabetes.[113] Pancreatitis (increased in this drug class) involves an acute inflammation. If this is prolonged, it causes pancreatic injury, which, in turn, becomes a risk factor for pancreatic cancer.[114]

Since pancreatitis cases increased with liraglutide, it is not surprising to find that pancreatic cancer cases increased as well. Two papers from the 1990s demonstrated that having pancreatitis presented a significantly increased risk of getting pancreatic cancer.[115,116]

Using the AERS database, Public Citizen found 28 cases of pancreatic cancer with liraglutide (February 2010 through September 2011): "pancreatic carcinoma" (n=22), "pancreatic neoplasm" (n=3), "adenocarcinoma pancreas" (n=3). By comparison, there was only one case (pancreatic carcinoma) for glipizide, another drug for diabetes — but 92 for exenatide, the other GLP-1R agonist.

D. Other serious neoplastic events

One of the pharmacological effects of liraglutide is raised insulin levels. When combined with the possible epidemiologic link between insulin and cancer, this provides an explanation for the observed higher rate of serious neoplastic events in clinical trials of liraglutide.[117,118] There is also the unexplored possibility that GLP-1, like GLP-2, can increase the growth of pre-existing precancerous lesions.[119] The question is, if an individual already has a pre-existing lesion, does treatment with a GLP-1 agonist result in an increase in neoplasms, as was the case with GLP-2 agonists? This has never been tested but might account for the increased rate of malignant neoplasms observed in the clinical trials (Table 17).

E. Renal toxicity

In May 2011, as a result of post-marketing reports of renal failure submitted to the FDA, a new warning was added to the liraglutide drug label stating that health care professionals and patients needed to be alert to signs of "acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis." Renal toxicity typically presents as nausea, vomiting, and diarrhea, all of which are common GI side effects of liraglutide, complicating diagnosis.

In January 2012, the first literature report appeared of a 53-year-old woman who had been on 1.8 mg/day liraglutide for one month and developed worsening GI symptoms. The authors were able to rule out other possible causes, and a kidney biopsy suggested the likely cause to be acute

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[113] Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterol. 2011;141:150-156.
[114] Jura N, Archer H, Bar-Sagi D. Chronic pancreatitis, pancreatic adenocarcinoma and the black box in-between. Cell Res. 2005;15:72-77.
[115] Bansal P and Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. Gastroenterol. 1995;109:247-251.
[116] Lowenfels AB, Maisonneuve P, Cavallini G., et al. Pancreatitis and the risk of pancreatic cancer. NEJM 1993;328:1433-1437.
[117] FDA Clinical Safety Review. Web page 152. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed February 14, 2012.
[118] Taubes G. Unraveling the obesity-cancer connection. Science 2012;335:28-32.
[119] Lakoubov R, Lauffer LM, Trivedi S, et al. Carcinogenic effects of exogenous and endogenous glucagon-like peptide-2 in azoxymethane-treated mice. Endocrinol. 2009;150:4033-4043.

tubular necrosis.[120] She recovered after discontinuation of liraglutide, volume repletion, and hemodialysis.

F. Hypersensitivity reactions

The reviewing division requested a medical officer consultation from the Division of Pulmonary, Allergy, and Rheumatology Products.[121] The resulting report highlighted several serious safety concerns regarding the allergenicity of liraglutide, noting that nearly 10% of liraglutide-treated subjects in the phase 3 clinical trials formed anti-drug antibodies (ADA), half of which showed cross-reactivity with native GLP-1. This resulted in the ADA-positive patients showing "trends toward an increased incidence in several categories of adverse events ... including infections (especially of the upper and lower respiratory tract) injection site reactions, and musculoskeletal disorders (e.g., arthralgias)."

The consultant added a warning that, "ADA formation with documented cross-reactivity to an endogenous protein carries a potential risk not only of inactivation of the native protein, but serum sickness, or other systemic hypersensitivity syndromes."

The FDA did include a statement in the liraglutide label under "Adverse Reactions," stating, "Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator treated patients (0.4%) in clinical trials."

However, because of technical issues with how the studies were done and the potential seriousness of the effects along with the incompleteness of the dataset, the consultant recommended a post-marketing study to address cutaneous and musculoskeletal manifestations. The consultant stated: "The outcome measures in this post marketing immunogenicity study should also address these immune mechanisms, including appropriate historical and physical assessments of target body systems (e.g., cutaneous and musculoskeletal manifestations), measuring complement levels as an index of immune complex mediated disease, and screening hepatic transaminases and renal function tests in the setting of systemic inflammatory in the setting of systemic inflammatory findings."

The FDA's approval letter for liraglutide[122] contains requests for Novo Nordisk to undertake a five-year epidemiological study that includes measurements of hypersensitivity (as well as hypoglycemia, pancreatitis, and overall malignant neoplasms) and a randomized, double-blind study (of unspecified length) that includes measurements of immunological reactions. Unfortunately, we do not know how much of the consultant's advice is being followed and will not have results until the final reports are submitted sometime in 2016 — and maybe not even then, because post-marketing study results are often not made public. Meanwhile, patients and their health care providers face unknown serious risks.

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[120] Kaakeh Y, Kanjee S, Boone K, Sutton J. Liraglutide-induced acute kidney injury. Pharmacotherapy 2012;32:e7-e11.

[121] Porter B. Medical officer consultation. Web page 6. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 17, 2012.

[122] FDA approval letter for liraglutide. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000approv.pdf. Accessed February 17, 2012.

G. Other potential indications being pursued by Novo Nordisk

1. Pediatric trials

There is one completed pediatric (ages 10-17 years) and adult (ages 18-45 years) safety/tolerability, pharmacokinetics and pharmacodynamics study of liraglutide, but data is not yet available.[123] These pediatric trials expose children to a drug that the FDA toxicology and clinical safety reviewers concluded should not even have been approved for adults because of unresolved serious safety issues.

As the FDA's Dr. Mahoney stated in reference to liraglutide's use in the adult population, "In the United States, there are already 11 classes of drugs approved for glycemic control in type 2 diabetes, and one other in this class [exenatide]. The need for new therapies for type 2 diabetes is not so urgent that one must tolerate a significant degree of uncertainty regarding serious risk concerns."[124] In light of this, there certainly should not be studies in the pediatric population. There is no excuse for exposing children to a drug for which so many known and unresolved safety issues exist: GI toxicity, pancreatitis, kidney failure, thyroid tumors, hypersensitivity reactions, and unknown effects on bone, because calcitonin binds to bone cells (osteoclasts).

2. Anti-obesity trials[125,126]

There is a concerted effort to expand the indications for liraglutide. Recently published obesity trials funded by Novo Nordisk employed doses up to 3.0 mg/day, a dose 1.7 times higher than the maximum dose currently used for treatment of diabetes. The first 20 weeks of the two-year obesity trial were randomized, double-blind, and placebo-controlled. However, between 20 and 52 weeks, the "sponsor/statistician" was unblended. After one year, all were unblinded. That trial had six groups of about 93 subjects per group. Groups included placebo, orlistat 120 mg orally three times per day, and liraglutide at doses of 1.2, 1.8, 2.4, and 3.0 mg per day.[127]

Although there was a dose-dependent weight loss effect, there were also dose-dependent increases in GI symptoms, especially nausea (which reached 48% at the 3.0 mg dose) (Table 16). Drug-induced nausea may be one important factor in weight loss, along with an effect of GLP-1 on the brain.

Clinicaltrials.gov lists several active trials testing liraglutide in the obese population.

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[123] http://clinicaltrials.gov/ct2/show/NCT00943501?term=NCT00943501&rank=1

[124] FDA Clinical Safety Review Web page 146. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf. Accessed February 17, 2012.

[125] Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int JObesity. 2011; online publication, 16 August 2011; doi:10.1038/ijo.2011.158. NCT00480909.

[126] Astrup A, Rossner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet. 2009;374:1606-1616.

[127] Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int JObesity. 2011; online publication, 16 August 2011; doi:10.1038/ijo.2011.158. NCT00480909.

Table 16. Adverse Events Reported in ≥5% of Subjects in Monotherapy Trials (26-Week Diabetes Study[128] Versus First Year of an Anti-Obesity Study[129])

	Liraglutide Diabetes Trial	Liraglutide Obesity Trial	
	1.2 + 1.8 mg	2.4 mg	3.0 mg
Adverse Event Term	**(%)**	**(%)**	**(%)**
Nausea	28	38	48
Diarrhea	17	13	15
Constipation	10	23	18
Vomiting	11	15	13
Decreased appetite	nd	9.7	8.6

* nd = no data

VIII. PUBLIC CITIZEN'S SPECIFIC REQUESTED ACTION

The FDA's frequent solution to serious safety issues identified with new drugs during development is to describe the risks in the drug label and hope that physicians and patients will pay attention to warning signs and significance. Although this strategy might be appropriate for drugs with a unique clinical benefit, for liraglutide, with no such clinical benefit and only modest sugar-lowering efficacy, such labeling changes merely delay the time until the drug must be withdrawn from the market, leaving an increasing number of patients at risk of serious harm.

A biologically plausible reason for the observed toxicity is that GLP-1 receptors are very widespread in human tissues: They have been found in lung, brain, stomach, kidney, pancreas, intestine, heart, and thyroid.[130,131] In the case of human thyroid, both malignant and normal tissue have been shown to contain these receptors.[132,133] GLP-1 is also important in bone metabolism: Mice lacking GLP-1Rs develop bone fragility as a result of increased bone resorption by osteoclasts.[134]

As can be seen by subsequent FDA safety alerts issued for acute pancreatitis, thyroid toxicity, and kidney failure over liraglutide's first year and a half of marketing, warnings have not succeeded in preventing serious adverse reactions. This is especially unfortunate because diabetics are already at increased risk for pancreatic and kidney toxicity. The increase in these

[128] Novo Nordisk Inc. Victoza drug label. Available at http://www.novo-pi.com/victoza.pdf. Accessed February 17, 2012

[129] Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int JObesity. 2011; online publication, 16 August 2011; doi:10.1038/ijo.2011.158. NCT00480909

[130] Wei Y, Mojsov S. Tissue-specific expression of the human receptor for glucagon-like peptide-1: brain, heart and pancreatic forms have the same deduced amino acid sequences. FEBS Let. 1995;358:219-224.

[131] Korner M, Stockli M, Waser B et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. J Nucl Med. 2007;48:736-743.

[132] Korner M, Stockli M, Waser B et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. J Nucl Med. 2007;48:736-743.

[133] Gier B, Butler PC, Lai CK et al. Glucagon like peptide-1 receptor expression in the human thyroid gland. J Clin Endocrinol Metab 2012;97:1-11.

[134] Yamada C, Yamada Y, Tsukiyama K, et al.The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology 2008;149:574-579.

adverse event reports is due in part to the fact that there is no easy way for either patients or their health care providers to know whether the common GI side effects are something to ignore or are indicative of serious toxicity that needs immediate attention.

In addition to pancreatic, thyroid, and kidney toxicity, there is a potential for serious adverse effects in pregnancy. Major fetal malformations (malformations affecting kidneys, blood vessels, and bones) were seen in animals exposed to extremely low levels of drug: Malformations were seen in rats and rabbits at 0.8 and 0.2 times, respectively, the human drug exposure (a 1.8-mg dose). The FDA should require that liraglutide have a pregnancy registry to enable the agency to track potential effects on human reproduction.

The number of prescriptions for liraglutide has been steadily rising, putting increasing numbers of patients at risk of adverse reactions to this drug (Figure 5). The increase in adverse reactions is seen in the continuing reports in the FDA's database, making it clear that the FDA's use of warnings is not sufficient protection**.** Figure 5 includes prescription data for the other FDA-approved GLP-1 agonist Byetta.

Figure 5. Prescription Data for GLP-1 Agonists

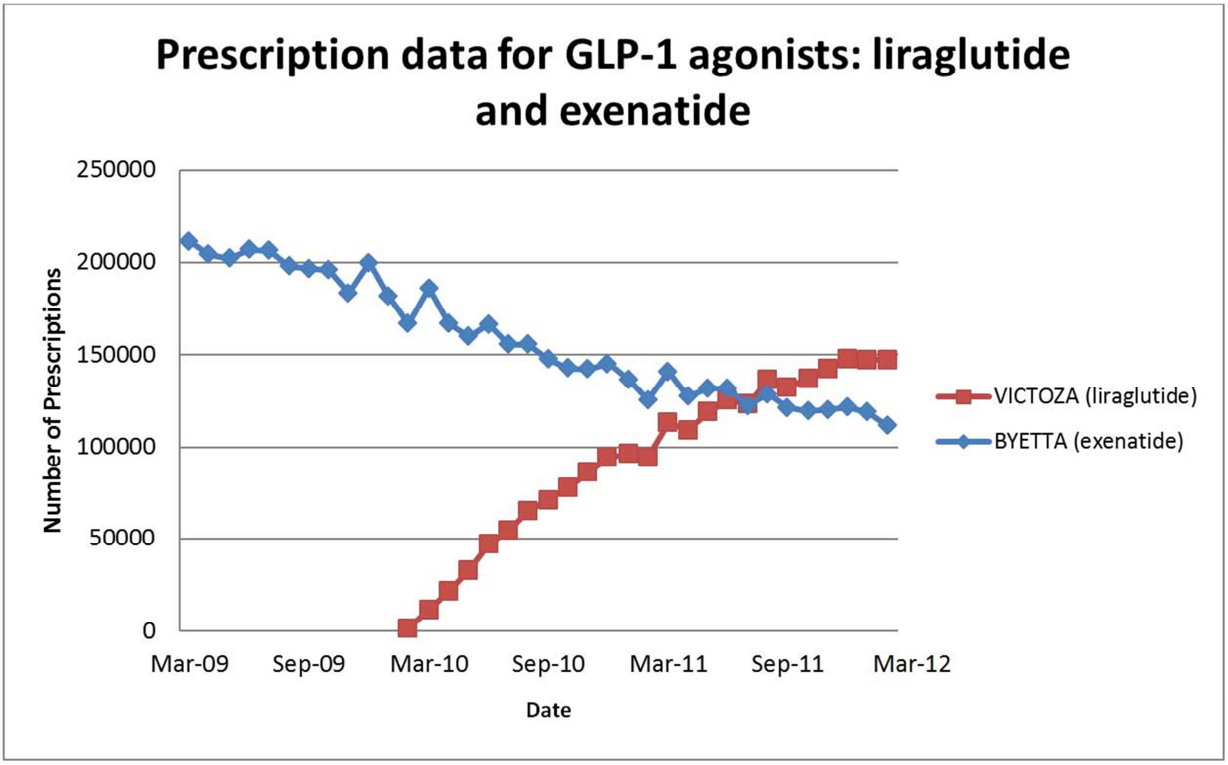

Table 17 summarizes the data for the increased risk that liraglutide poses for patients. The use of a higher dose (3.0 mg) to treat obesity will only increase these multiples.

Table 17. Summary of Rates of Serious Adverse Events in Phase 3 Clinical Trials

Adverse Event	Liraglutide: Rate per 1,000 Patient Years	Non-liraglutide: Rate per 1,000 Patient Years	Ratio of Liraglutide to Non-Liraglutide Event Rates
Papillary thyroid cancer	2.1	0.7	**3.0x**
C-cell hyperplasia	1.7	0.7	**2.4x**
Any thyroid neoplasm (serious & nonserious)	9.8	4.4	**2.2x**
Total serious neoplastic events	12.3	8.1	**1.5x**
Malignant neoplasms	10.7	8.1	**1.3x**
Pancreatitis	2.2	0.6	**3.7x**

Several of the FDA's own reviewers of the safety data concluded that a combination of serious safety issues, coupled with a lack of unique efficacy, meant that this drug should never have been approved. Public Citizen completely agrees with the opinions of those reviewers. As they pointed out, there are 11 classes of drugs available for treating diabetes. Since liraglutide provides neither unique nor significant advantages but only a complex collection of toxicities, it should be removed from the market. The potential for serious harm requires immediate withdrawal by the FDA to avoid putting more patients at risk.

In conclusion, Public Citizen hereby petitions the FDA, pursuant to the FDCA 21 U.S.C. § 355(e) and 21 C.F.R. 10.30, to immediately ban liraglutide (Victoza; Novo Nordisk).

IX. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

X. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Elizabeth Barbehenn, Ph.D.
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Sidney M. Wolfe, M.D.
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